

TRITON
19-I-0133

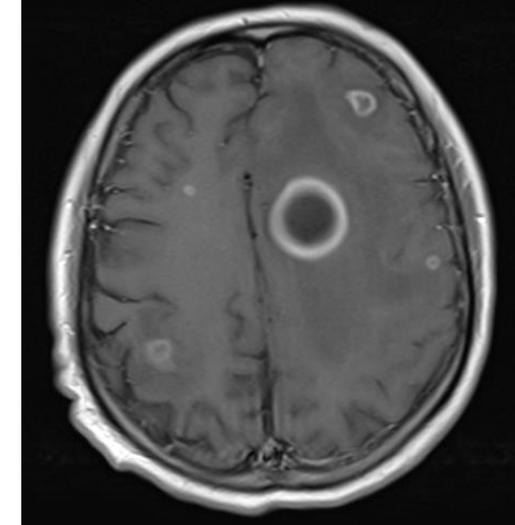
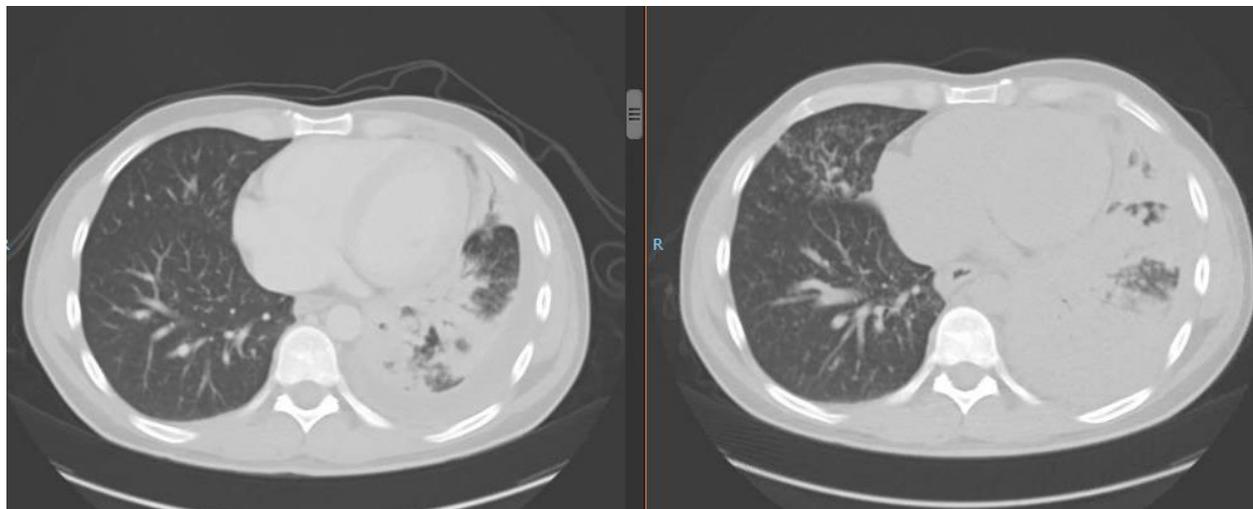
Paradoxical Tuberculosis Reactions
in Patients without HIV Infection



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HIV Pathogenesis Section

Paradoxical TB reaction

- Phenomenon that has been clinically observed in the literature since at least 1955
- Clinical and/or radiologic worsening of a patient's pre-existing TB while receiving anti-TB medications
 - Occurs in 6-30% of TB infected patients
 - Seen in both HIV infected and uninfected patients
 - Observations are seen in patients treated with TNF- α inhibitors
 - Can lead to increased morbidity and mortality (especially in patients with CNS TB)



Garcia Vidal. CID 2005

- **Range of presentations: Fever, CNS, LNs, Pulmonary**
 - Worsening lymphadenopathy common presentation
 - Patients with HIV (or with immune suppression) at higher risk
- **Predictors of presentation**
 - HIV status, Other types of immunosuppression, Disseminated disease (presence of LAN/positive cultures)
- **Timing of presentation varies**
 - Median of 4 weeks (HIV positive) to 8-12 weeks (HIV negative) from ATT

Paradoxical TB reaction

- **Outcomes**

- Overall favorable
- Patients with increased lymphadenopathy at times required surgical drainage and corticosteroids

- **CNS TB**

- Intracranial tuberculomas progressing leading to clinical deterioration
- Can require increased immunosuppression with steroids, thalidomide
- Residual deficits and even death

Paradoxical TB Reaction

- Worsening of TB manifestations after initiation of TB medication
- Incidence 6-30%
- Initial improvement with TB medications
- Predictors
 - HIV positivity/Immunosuppression
 - Disseminated disease/LAN

Immune Reconstitution Inflammatory Syndrome (IRIS)

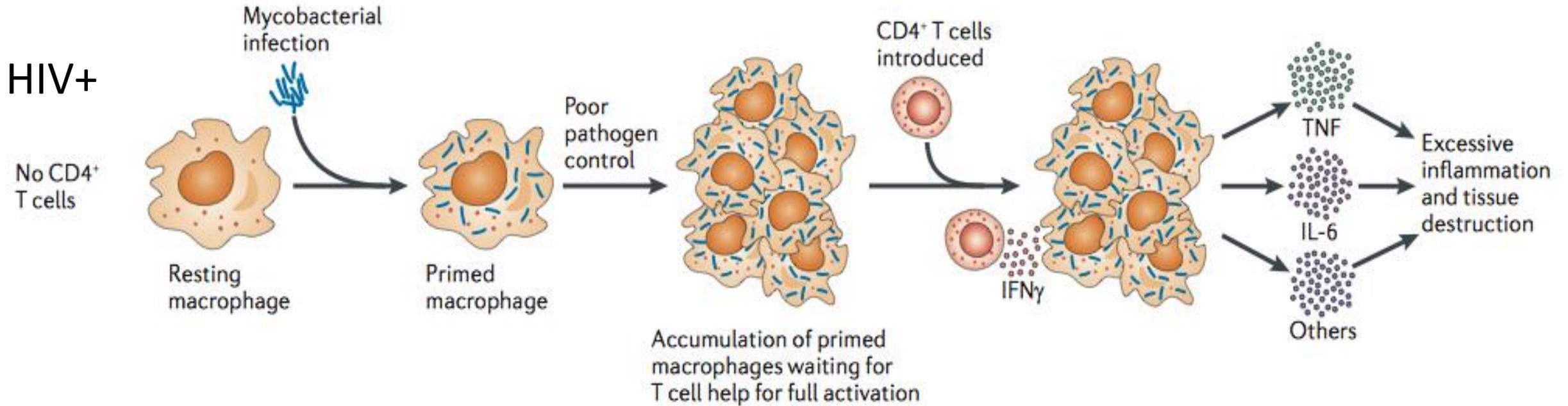
- Worsening of manifestations or an abrupt/atypical presentation of infection when HIV patients start ARVs
- Incidence 7-50%
- Successful HIV virologic suppression and microbiologic outcome (paradoxical)
- Predictors:
 - CD4 lymphopenia
 - Pre-existing OI
 - Shorter treatment of OIs pre-ART

Pathogenesis of Paradoxical TB Reactions

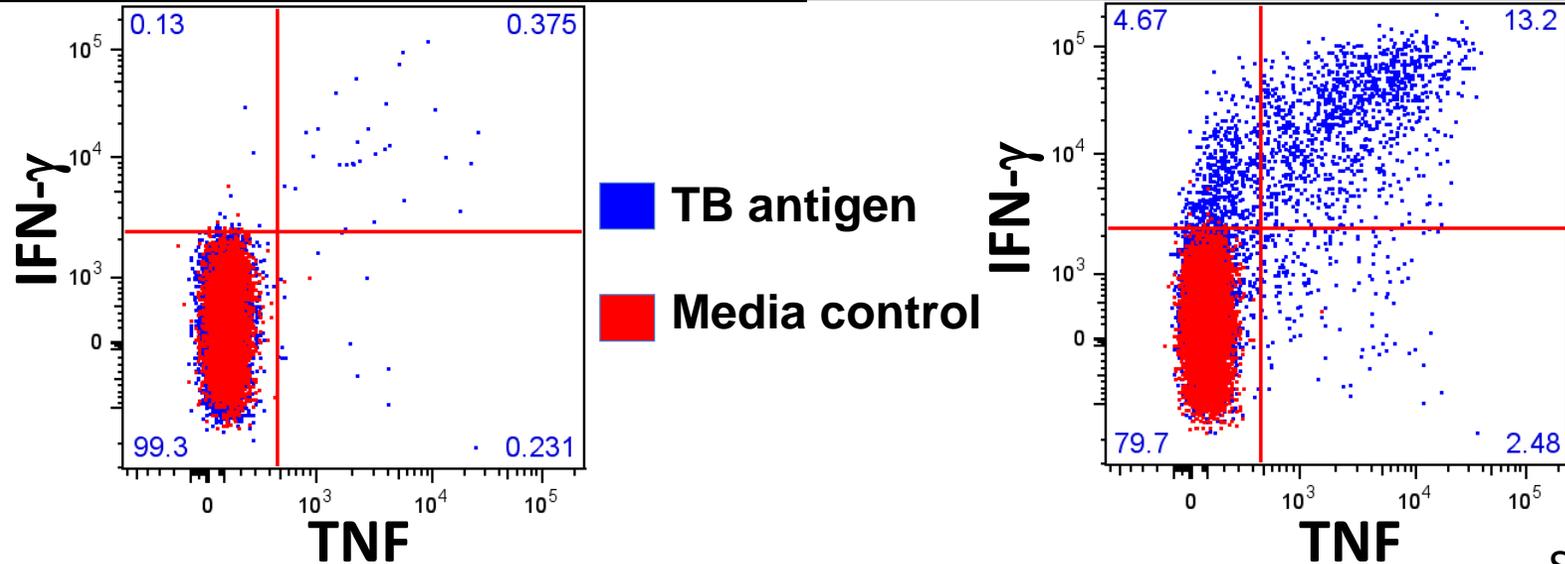
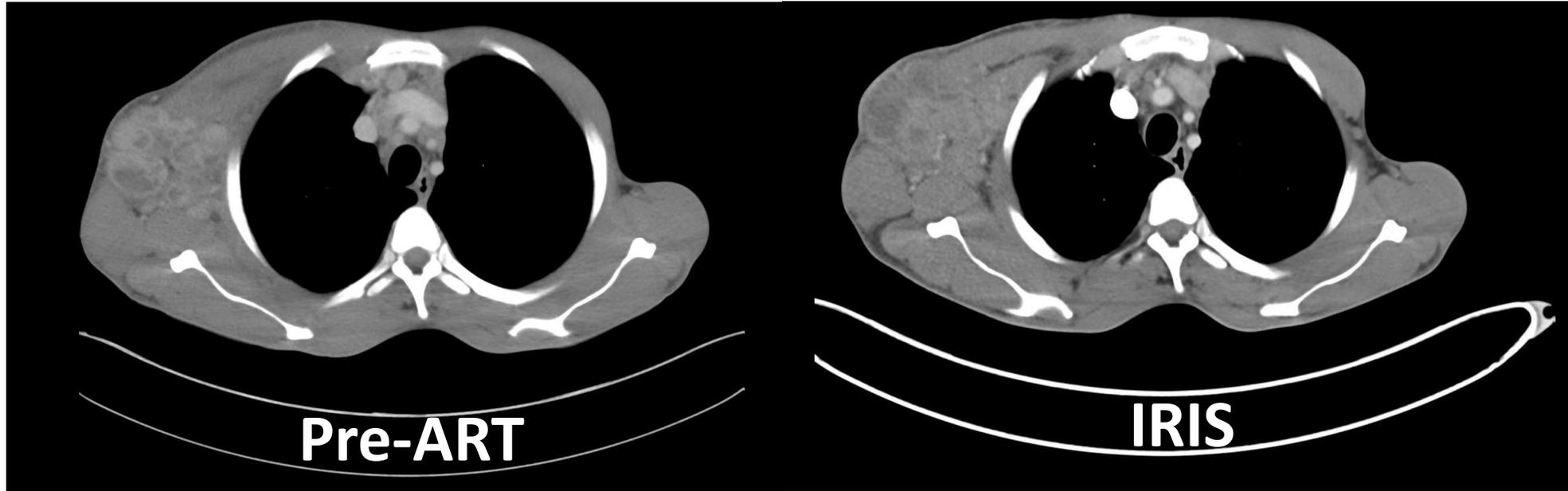
- Current literature primarily consists of clinical observations at this time
 - Role of immunodeficiencies/immune dysregulation
 - Steroid Tapering versus HIV, Infliximab, AutoAbs, TB itself?
 - Observation of increased lymphocyte counts

- Pathogenesis investigation has been primarily in IRIS
 - Exuberant T cell responses
 - Reliant on interplay with myeloid cells (higher proportion of classical monocytes, cytokines associated with monocytes)
 - Evidence of inflammasome activation

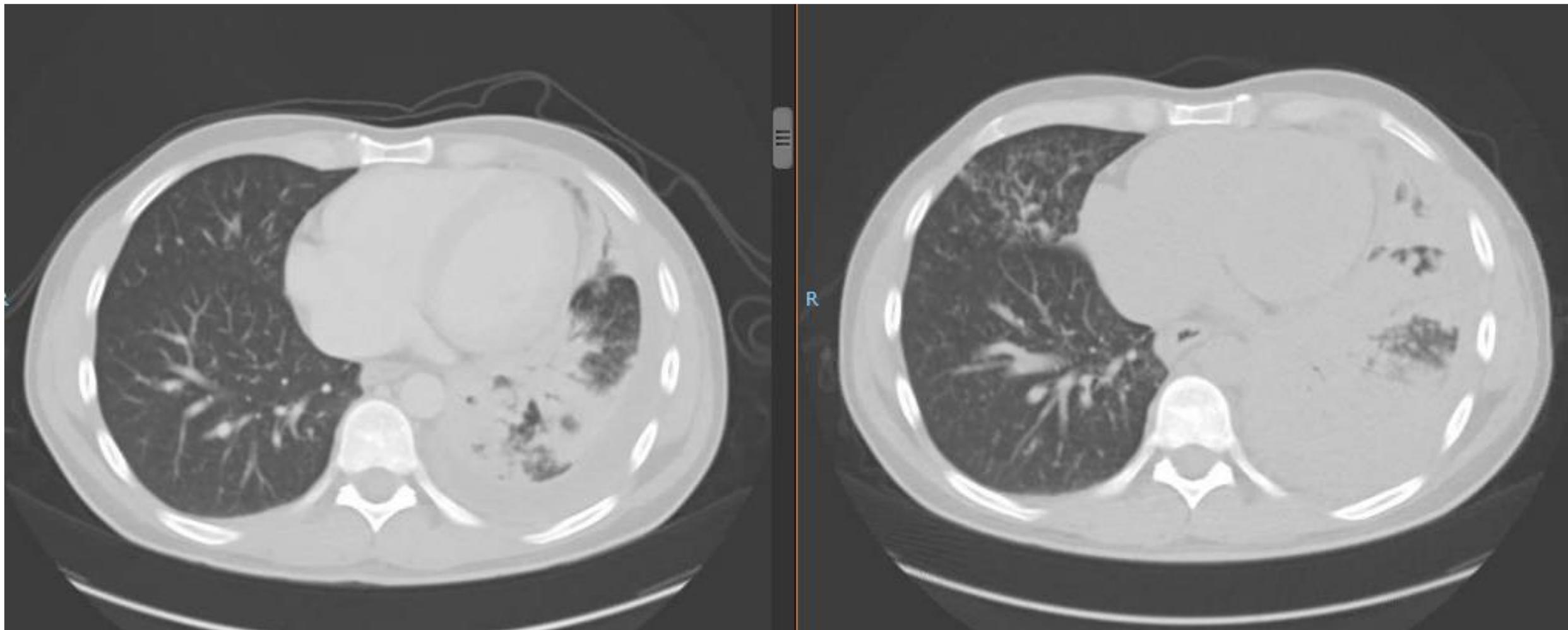
Immune reconstitution meets infection... IRIS



Case of TB IRIS: role of T cells



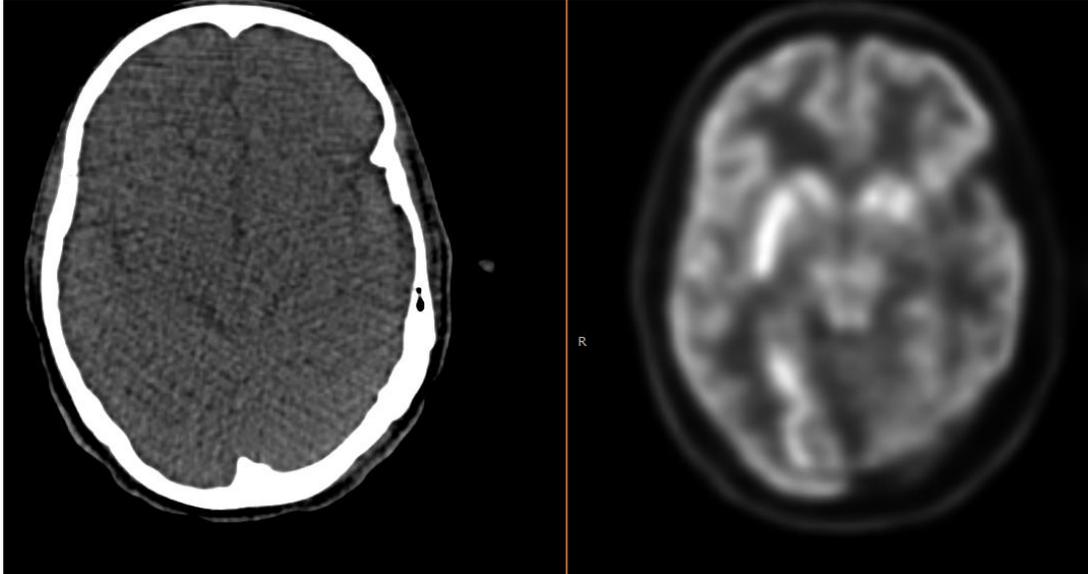
Case 1: 36 year old male with HIV+ and TB



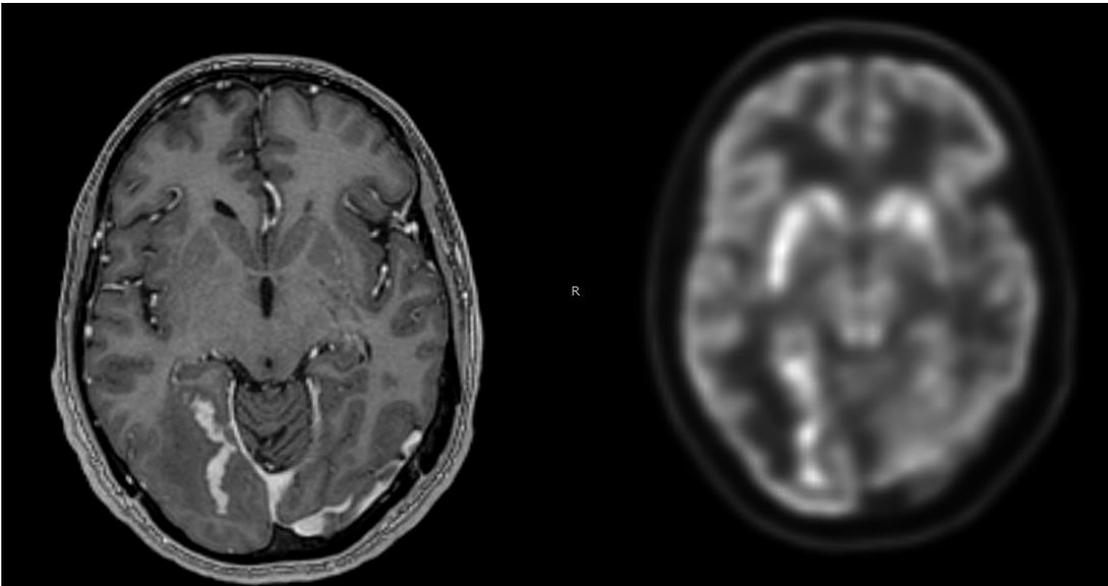
Screening

Day 1 ARV

Case 1: 36 year old male with HIV+ and TB

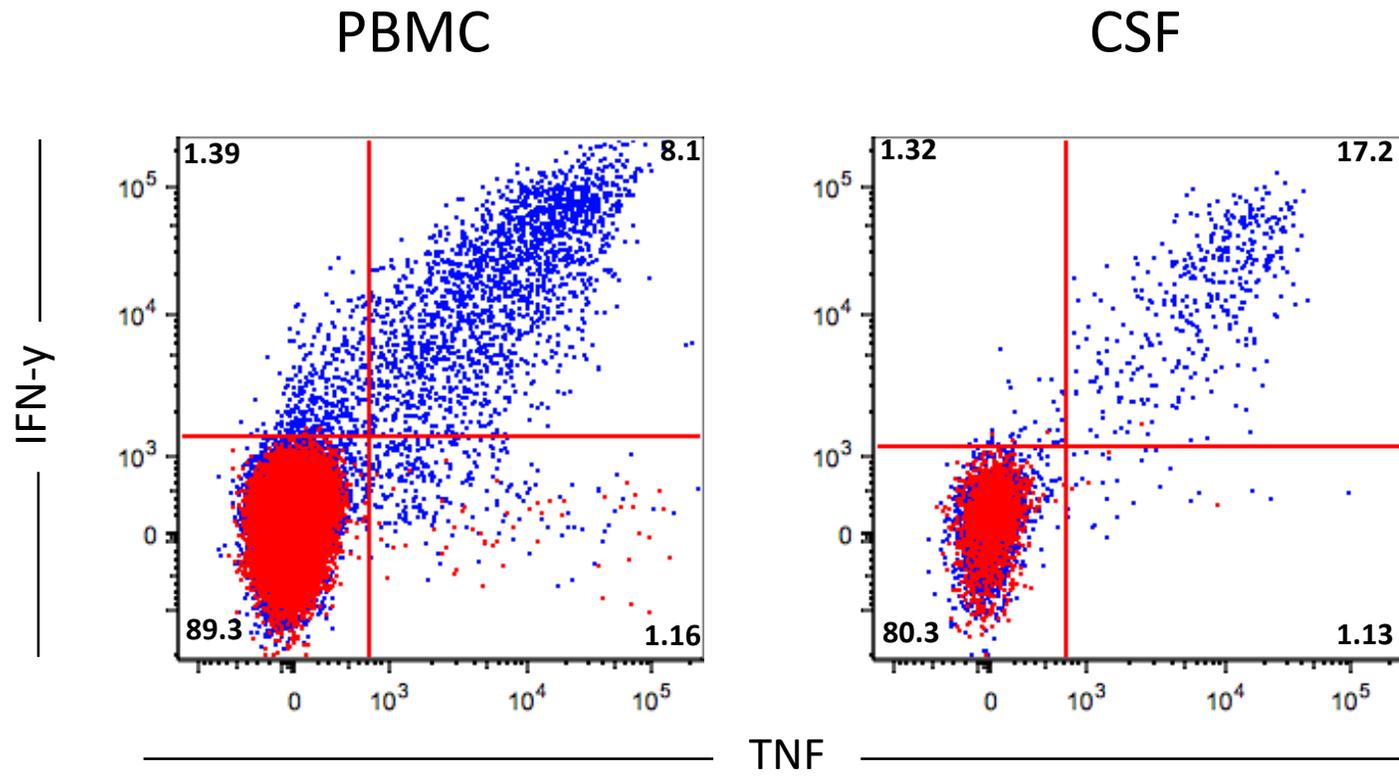


4/15/2015

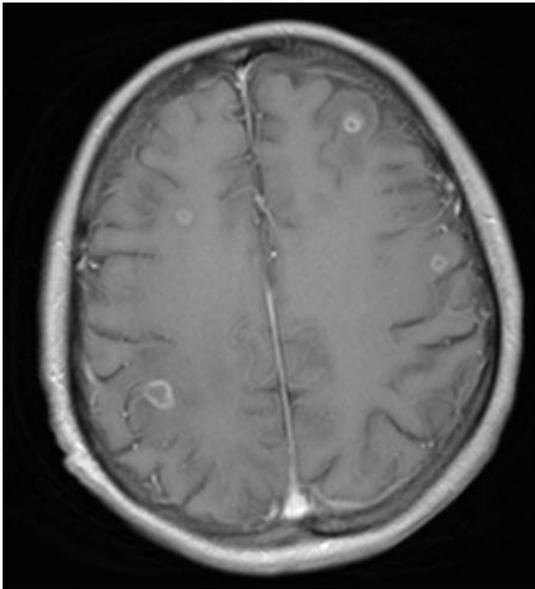


5/22/2015

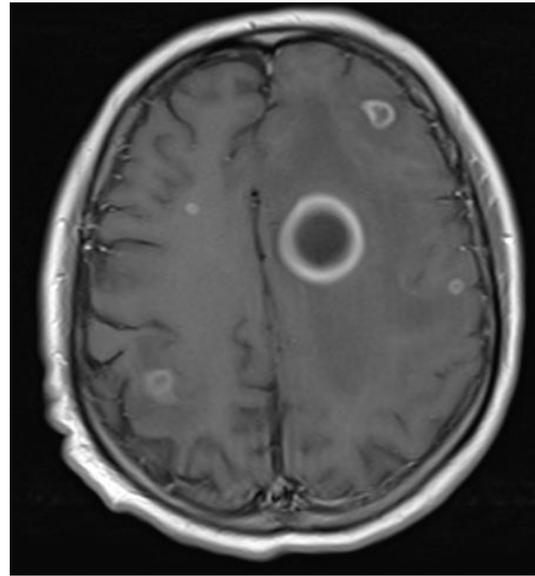
Case 1: T cell stimulations



Case 2: 39yoM with CNS TB

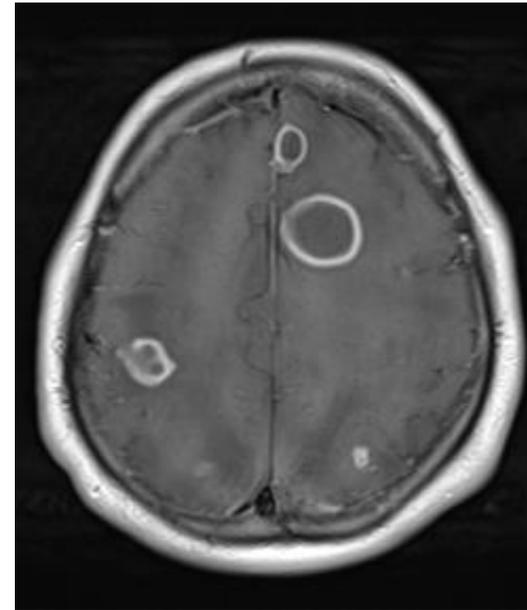


Initial Presentation



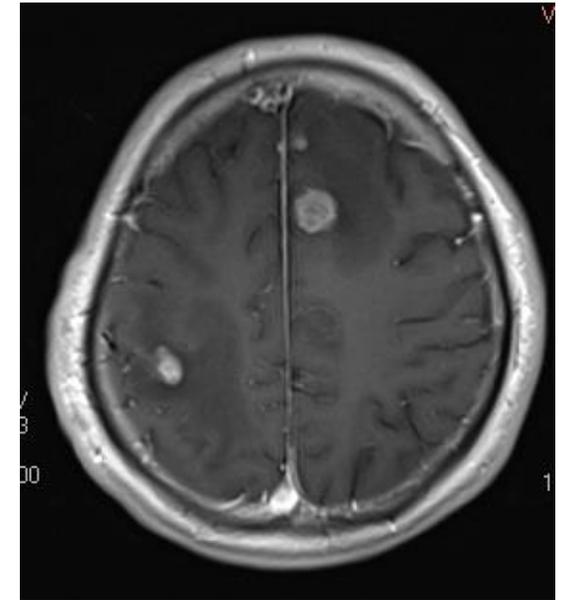
3 months of ATT

- New Seizures



6 months of ATT

- New Seizures
- On Dexamethasone
- Intensification of ATT



~ 2 years at NIH

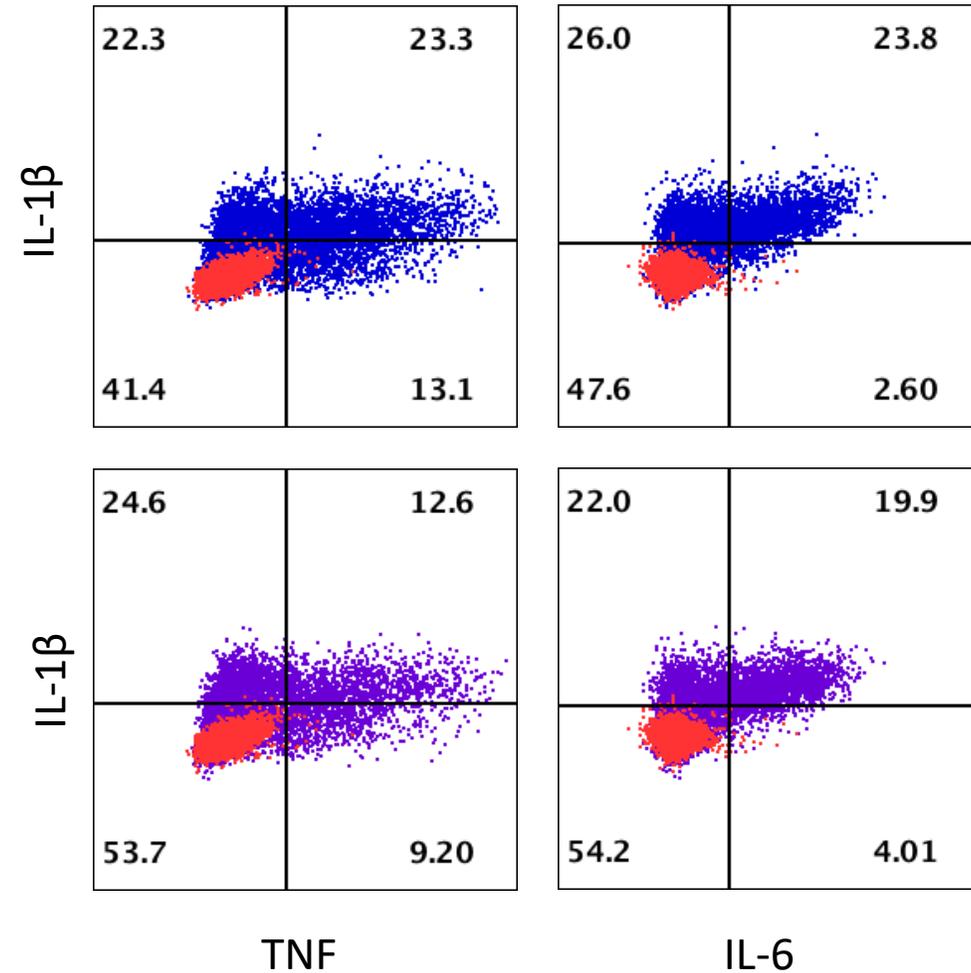
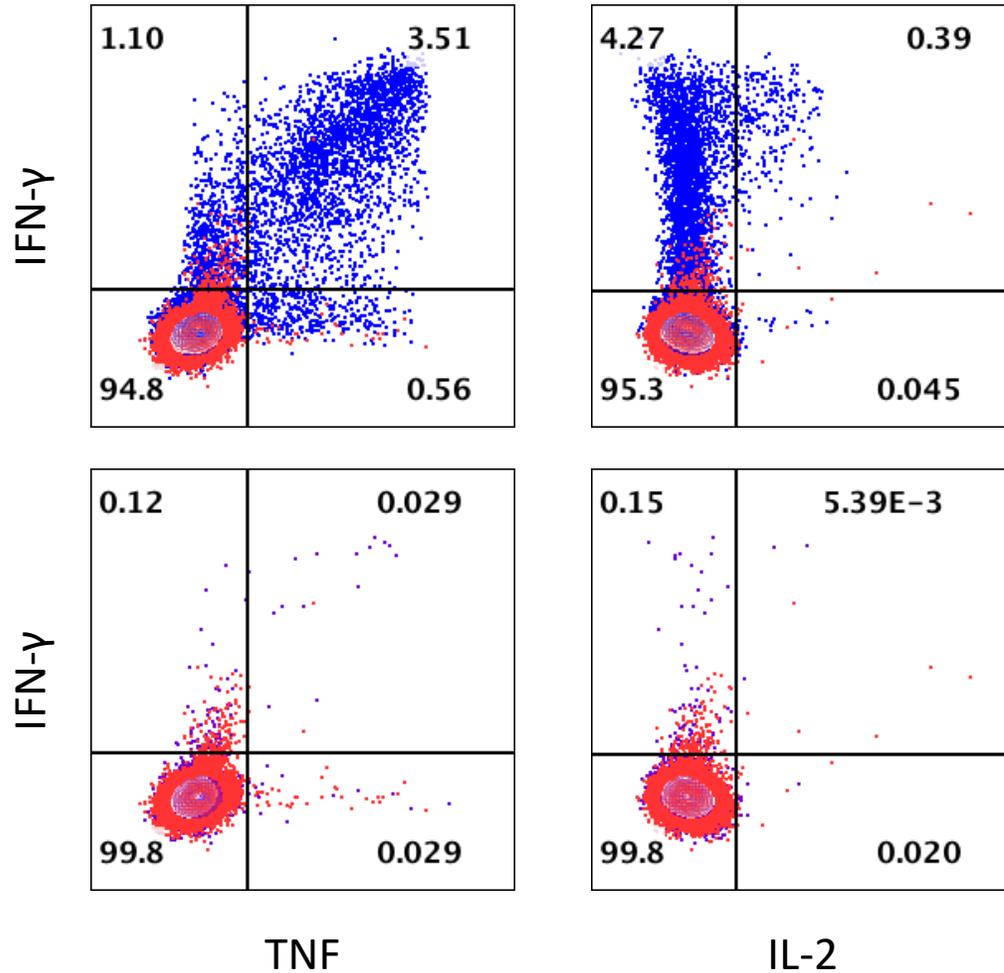
- Slow Taper
- Returned to work

Case 2:

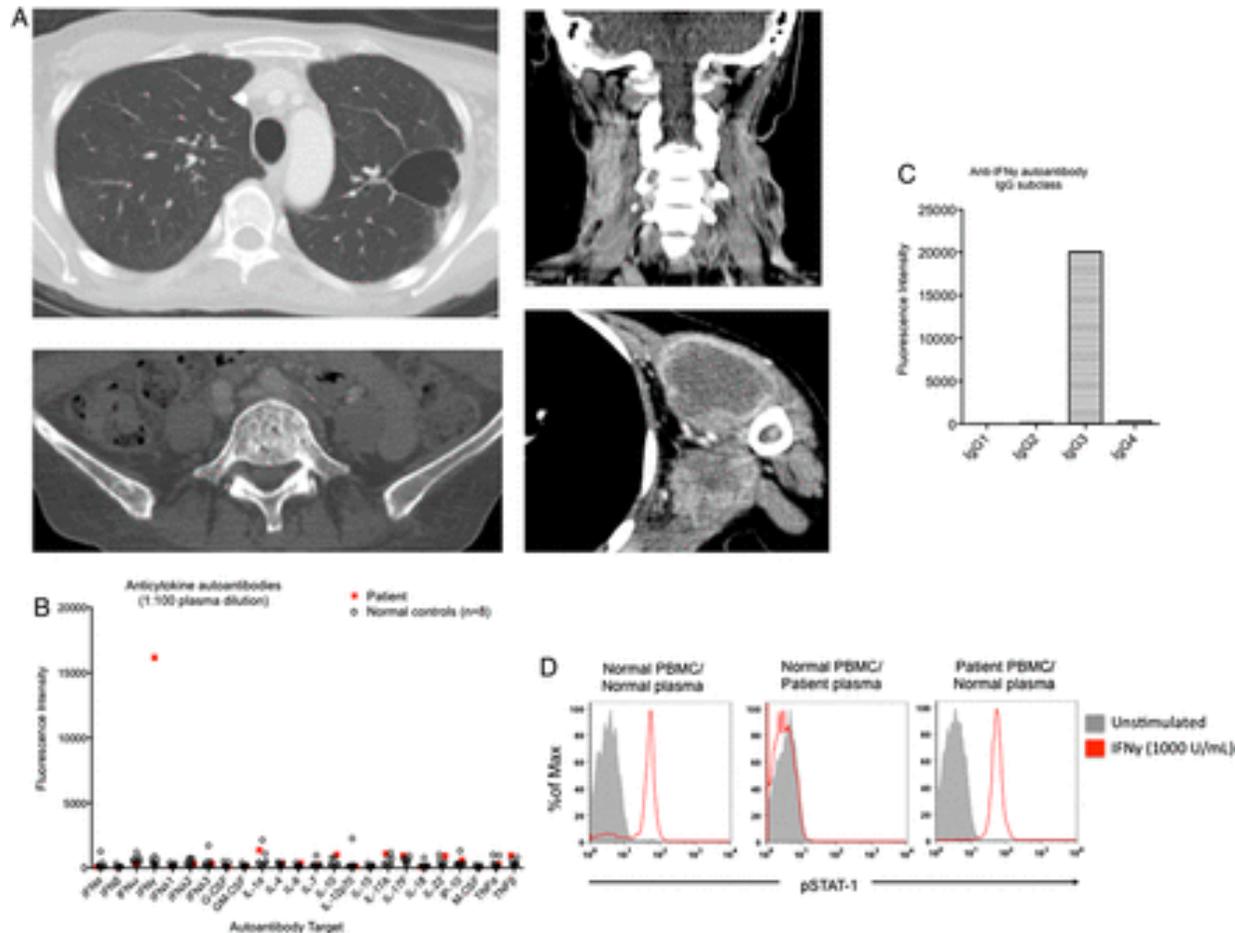
Media only
PPD/irradiated TB
CMV pp65/CMV lysate

T cell stimulation

Monocyte stimulation



Case 3: 55yoF with Disseminated TB



- 55yo Thai lady initially presented with respiratory failure and sepsis and found to have right lung opacification
- 4 weeks later diagnosed with TB with biopsy of cervical adenopathy in setting of fevers and chills
- Two weeks of ATT, developed fevers, malaise, and new left upper lobe cavity
- 11 weeks into therapy developed large draining abscesses, bone lytic lesions, and liver lesions
- Workup found to have auto-antibody to IFN- γ

Paradoxical TB reactions

- Pathogenesis is not well understood
 - Primarily clinical characterization without immunologic workup
 - Clinical patterns of paradoxical TB reactions
 - Cases demonstrating an exuberant T cell response at time of reaction
- Diagnosis is made by excluding other causes for worsening TB
- Distinguishing between a paradoxical reaction and treatment failure is important for appropriate management
- Confirming a poor response to anti-tuberculous therapy can be challenging with the time needed to grow TB and difficulty of culturing from extrapulmonary sites

Paradoxical TB reactions: Triton Study



Triton.

- Goal is to improve understanding of the pathogenesis of this paradoxical reaction in order to assist with diagnosis and treatment options.
- Hypothesis:
 - Pathogenesis driven by immune dysfunction being driven by a high burden of mycobacterial disease and restoration of immune responses upon starting ATT.
 - Immune suppression by TB itself
 - Withdrawal of immune suppression or low drug levels

TRITON: Paradoxical Tuberculosis Reactions in Patients without HIV Infection



Triton.

- Objectives

- Characterize immunologic and radiographic responses of TB patients with paradoxical reactions.
- Investigate whether biomarkers and/or microbiologic burden (using PET and research TB antigen) correlate with paradoxical reactions
- Exploratory: Drug levels, Auto-antibody production, Transcriptomic studies to look for host predisposition

TRITON: Paradoxical Tuberculosis Reactions in Patients without HIV Infection



Triton.

- Case Based ARM and Prospective Cohort ARM
 - Criteria for Case Based ARM: Confirmed TB, ATT for 2 weeks, Signs/Symptoms of Paradoxical TB reaction
 - Criteria for Prospective Cohort ARM: Presenting 2 to 4 months after starting ATT to match timing of paradoxical reactions
 - Exclusion HIV infection, pregnancy, breastfeeding, conditions that limit participants ability to participate in research
- Procedures: Blood draws, apheresis, sputum, PET/CT
- Follow Up: 3 protocol visits (with additional clinical visits as needed for management of issues related to Paradoxical TB reactions)

TRITON: Paradoxical Tuberculosis Reactions Patients without HIV Infection



Triton.

- Estimated enrollment is 60, 20 in Case Based ARM and 40 in Prospective Cohort
- For eligible patients, please contact:
 - Maura Manion, MD PI (maura.manion@nih.gov)
 - Frances Galindo, RN SC (france.galindo@nih.gov)
- For HIV+ patients with naïve to ART or with suspected IRIS, please consider PANDORA protocol

Acknowledgements

HIV Pathogenesis Section

- Irini Sereti, Chief
- Frances Galindo
- Elizabeth Laidlaw
- Luxin Pei
- Nuha Naqvi
- Chun-Shu Wong
- Silvia Lage
- Safia Kuriakose



NIH Associate Investigators

- Ray Chen
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